REMARKS

Claims 1, 3-4, 9-13, 15-20, 22-23, 28-31, 33-37, 40, and 45-46 are pending in the application. Claims 2, 5-8, 14, 21, 24-27, 32, 38-39, 41-44, and 47-50 are canceled without prejudice. Claims 11-13, 15-19, 29-31, 33-37, and 40 are withdrawn from consideration. Claims 1, 3, 4, 9-10, 20, 22, 23, 28, and 45-46 are under examination.

By the present Amendment, Claims 1, 3, 9, 20, 22, and 45 are amended for clarity and to correct errors in antecedent basis. None of these amendments introduce new matter into the application. Reconsideration of the application, in view of these amendments and the following remarks, is respectfully requested.

Patentability under 35 U.S.C. § 112, First Paragraph

Withdrawal of Previous Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner is thanked for notifying Applicant that the previous rejection of Claims 1-4, 9-10, 20-23, 28, 38-39, and 45-46 under 35 U.S.C. § 112, first paragraph is withdrawn.

Pending Rejection under 35 U.S.C. § 112, First Paragraph

Claim 28 stands rejected under 35 U.S.C. § 112, first paragraph as allegedly non-enabled. The Examiner alleges that the particular *Salmonella* strains recited in Claim 28 would be required to practice the invention, and that the particular strains "must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public." (*see* Office action, pp. 2-3). The Examiner notes that the enablement requirement "may be satisfied by a deposit of the *Salmonella typhimurium* LVR01, LVR03, and SL3261, *Salmonella enteritidis* LVR02, and *Salmonella typhi* CVD915 strains."

Applicant respectfully requests that this rejection be held in abeyance until one or more Claims are found to be allowable (*see* 37 C.F.R. § 1.804(a)). Upon allowance, Applicant will make and/or document an acceptable deposit of the biological organisms encompassed by one or more allowed Claims in accordance with the relevant rules (*see* 37 C.F.R. § 1.809(b)(1)), should such Claims be pending at the time of allowance.

Patentability under 35 U.S.C. § 103(a), Non-obviousness

Withdrawal of Previous Rejections under 35 U.S.C. § 103(a)

The Examiner is thanked for notifying Applicant that the following previous rejections under 35 U.S.C. § 103(a) have been withdrawn: (1) Claim 4 over Bachmann in view of Benkirane, (2) Claims 9 and 10 over Bachmann in view of Clemens and Kleanthous, (3) Claims 20, 22, 28, and 45 over Bachmann in view of Lu and Chabalgoity, and (4) Claims 23 and 46 over Bachmann in view of Lu and further in view of Benkirane.

Pending Rejections under 35 U.S.C. § 103(a)

Claims 1, 3, and 9 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Bachmann, U.S. Patent Publication No. 2003/0219459 [Bachmann] in view of Gizurarson *et al.*, U.S. Patent No. 6,514,503 [Gizurarson]. The Examiner cites Bachmann for allegedly disclosing a composition comprising a mammalian prion protein corresponding to SEQ ID NO: 4 and the adjuvant aluminum hydroxide, which is capable of eliciting a humoral immune response. The Examiner concedes that Bachmann fails to teach a composition that is "suitable for mucosal administration and elicits a humoral immune response that is predominantly associated with an IgA response when administered to [the] mucosal immune system." The Examiner alleges that Gizurarson remedies this deficiency in Bachmann by disclosing "compositions comprising prion proteins suitable for mucosal administration" through "enhanced adhesion of the antigen to the mucosal membrane and enhance[d] absorption of the antigen through the mucous membrane." The Examiner further alleges that Gizurarson teaches that mucosal administration elicits secretory antibodies of the IgA isotype. Thus, the Examiner alleges that "it would have been obvious to provide Bachmann's composition comprising prion proteins for mucosal administration as taught by Gizurarson."

Applicant respectfully traverses the present basis for rejecting Claims 1, 3, and 9 under 35 U.S.C. § 103(a). Obviousness is determined in accordance with the inquiry the court set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966) which involves factual findings of: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the Claimed subject matter and the prior art; and, when relevant, (4) objective evidence of non-obviousness. *Beckson Marine, Inc.*, 292 F.3d at 725-26. While the

obviousness inquiry should look beyond the specific problem that the patentee was trying to solve, and includes, at the time of the invention "a known problem for which there was an obvious solution encompassed by the patent's Claims," such is not the case for the presently Claimed invention. *KSR International v. Teleflex Inc.*, 127 S.Ct. 1727, 1742 (2007).

Claim 1, as presently amended, is directed to a composition comprising an isolated mammalian prion protein and an antigen carrier or delivery vehicle. The isolated mammalian prion protein is selected from the group consisting of a bovine, deer, elk, and sheep prion protein; the composition is suitable for mucosal administration; and the composition elicits a humoral immune response that is predominantly associated with a mucosal IgA response and any concomitant immunoglobulin counterpart in other bodily fluids when introduced to a mammalian mucosal immune system. Each of Claims 3 and 9 depend from and further limit the scope of independent Claim 1. Thus, the non-obviousness of Claims 3 and 9 necessarily follows from the non-obviousness of Claim 1.

Bachmann is directed, generally, to conjugates that include a prion protein (PrP) and a virus-like particle (VLP). Recognizing the challenge of inducing an antibody response to self-molecules by conventional vaccination, Bachmann teaches that "[o]ne way to improve the efficiency of vaccination is to increase the degree of repetitiveness of the antigen applied. Unlike isolated proteins, viruses induce prompt and efficient immune responses in the absence of any adjuvants both with and without T-cell help." (P. 2, ¶ 12). Bachmann further states that "[f]or soluble antigens present at low concentrations, this is due to tolerance at the Th cell level. Under these conditions, coupling the self-antigen to a carrier that can deliver T help may break tolerance. … B cell tolerance may be reversible (anergy) and can be broken by administration of the antigen in a highly organized fashion coupled to a foreign carrier." (P. 2, ¶ 13).

Thus it is clear that Bachmann is directing the skilled artisan to the use of protein/virus-like particle conjugates to induce an immune response and that this reference teaches away from the use of isolated proteins by expressly teaching that isolated proteins, including isolated prion proteins, are inefficient at eliciting an immune response. Rather, Bachmann teaches that prion proteins "bound to a core particle having a structure with an inherent repetitive organization, and … in particular to virus-like-particles (VLP's) and subunits

of VLP's ... leading to highly ordered and repetitive conjugates represent potent immunogens for the induction of antibodies specific for PrP. ... This therapeutic is able to induce high titers of anti-PrP antibodies in a vaccinated animal." (P. 2, ¶ 14). Bachmann's teachings are clearly directed to prion-VLP conjugates; Bachmann is silent with respect to compositions comprising an isolated mammalian prion protein.

Moreover, Bachmann fails to teach or suggest compositions comprising aluminum hydroxide (alum) for mucosal delivery as recited in the instant Claims. On the contrary, Bachmann's sole reference to alum is within the context of prion-VLP conjugates for parenteral administration. For example, in the legend for Figure 3 and within corresponding Example 15, Bachmann states that "50 μg of mPrPs-Qβ and 50 μg of mPrP1-Qβ were administered in alum" (P. 4, ¶ 35) and that "50 μg mPrPs-Qβ or mPrPl-Qβ were applied intraperitoneally in 500 μl (1 mg) alum or subcutaneously as CFA-emulsion (100 μl) on day 0 or intraperitoneally as IFA-emulsion (100 μl) on day 14 and day 28." (P. 36, ¶ 440). Clearly, Bachmann did not contemplate the use of alum for mucosal delivery of its prion protein-VLP conjugates, much less the use of alum for mucosal delivery of an isolated prion protein as provided by the instant claims.

In fact, as Applicants discovered as part of the present invention, the use of alum for mucosal delivery derives from the formation of a gel that maintains the isolated prion protein in an alkaline pH that speeds, in certain mammals, the passage through the stomach, promoting an early opening of the pylorus and the delivery of the contents to the intestines with minimal damage from the acid environment of the stomach. Because of the viscous gel-like formulation, the passage in the intestines is slowed thereby facilitating the uptake of the isolated prior protein by cells of the mucosal immune system. These features of the claimed invention were not recognized by Bachmann. Consequently, the presently claimed compositions comprising an isolated mammalian prion protein and an antigen carrier or delivery vehicle could not have taught or suggested by this reference.

In summary, Bachmann fails to teach or suggest the presently claimed invention because, *inter alia*, Bachmann only teaches the parenteral administration of compositions comprising a prion protein-VLP conjugate and alum. Bachmann is silent about eliciting an IgA

response by the mucosal administration of an isolated mammalian prion protein in combination with alum.

Gizurarson does not remedy these deficiencies in the Bachmann reference. On the contrary, Gizurarson is directed to compositions comprising "an antigen and an adjuvant containing 0.01-70% v/v of glycerides selected from the group consisting of monoglycerides, diglycerides, and mixtures thereof." Col. 2, line 67 through col. 3, line 2. The term alum never appears in the Gizurarson reference.

Moreover, Gizurarson is silent about compositions comprising a prion protein or any other self antigen. For example, at col. 6, lines 55-64, Gizurarson teaches that:

> The antigen can be selected from the group including, but not limited to, tetanus toxin, influenza virus, diphtheria toxoid, HIV gp120, IgA-protease, insulin peptide B, vibriose, salmonella, *Spongospora subterranean*, respiratory syncyctial virus (RSV) (e.g., an RSV subunit vaccine), *Haemophilus influenza* outer membrane proteins, *Helicobacter pylori* urease and recombinant pilins of *Neisseria meningitides* and *N. gonorrohoeae*, or a portion thereof which retains the ability to stimulate an immune response.

Nowhere within Gizurarson does this reference discuss the mucosal administration of an isolated mammalian prion protein.

While Gizurarson teaches the mucosal delivery of compositions comprising a glyceride and a non-self (*i.e.* foreign) antigen, this reference is silent about the mucosal delivery of a composition comprising an antigen carrier or delivery vehicle, including alum, and a self antigen, such as an isolated mammalian prion protein as recited in the instant Claims.

In fact, at the time of the presently Claimed invention, it was well accepted in the art that the mucosal administration of a self-antigen, such as a prion protein, would lead to immune tolerance to that antigen – which is quite the opposite of eliciting a humoral IgA immune response. See, *e.g.*, Czerkinsky *et al.*, "Mucosal Immunity and Tolerance: Relevance to Vaccine Development" *Immunological Reviews* 170:197-222 (1999) (copy attached). For example, Czerkinsky teaches that "[e]qually important to host immune defense is the capacity of [mucosa-associated lymphoid tissue] MALT to promote specific immunological unresponsiveness (tolerance) after natural or deliberate mucosal exposure to a variety of antigens. This form of

tolerance is considered as a major adaptive immune defense mechanism whereby we avoid developing harmful immune responses against the plethora of dietary and airborne antigens encountered each day." P. 198 col. 2, lines 22-28. Cleary, it was not contemplated that mucosal administration of a self-antigen would lead to the stimulation of an IgA response.

Thus, at the time of the present invention, it could not have been obvious to combine an antigen carrier or delivery vehicle, such as alum, and any self-antigen, such as an isolated mammalian prion protein, to generate the compositions of the presently claimed invention, which are suitable for mucosal administration and for eliciting a humoral immune response (*i.e.* Th2-mediated antibody response), including an IgA response. On the contrary, one skilled in the art would have been led away from the presently Claimed invention because they would have believed, based on the teachings of Czerkinsky, that the mucosal administration of a composition comprising alum and an isolated prion protein would have led to immunological unresponsiveness (*i.e.* tolerance), which is the opposite effect as achieved by the presently claimed compositions.

With respect to Claim 3, the Examiner alleges that the claim "recites an open language with regard to the sequences represented by residues 93-156 and 123-225 of the SEQ ID NO: 4." As noted above, and without acquiescing in the present basis for rejection, by the present Amendment, Claim 3 is amended to replace the open ended language "comprises" with the closed language "consists of." Accordingly, the isolated prion proteins of Claim 3 do not read on a full-length prion protein. Thus, the present amendment to Claim 3 obviates this basis for rejecting over Bachmann in view of Gizurarson.

Applicants respectfully request reconsideration and withdrawal of the present basis for rejection of Claims 1, 3, and 9 over Bachmann in view of Gizurarson.

Claim 4 stands rejected under 35 U.S.C. § 103(a) as allegedly obvious over Bachmann and Gizurarson as applied to Claim 1, above, further in view of Benkirane *et al.*, *J. Bio. Chem.* 268:26279-26285 (1993) [Benkirane]. The Examiner alleges that Bachmann and Gizurarson teach a composition comprising a mammalian prion protein for mucosal administration, wherein the prion protein sequence is identical with the presently claimed SEQ ID NO: 4." The Examiner concedes that "[n]either Bachmann et al. nor Gizurarson et al. teach

the prion protein wherein all amino acids are D-amino acids." The Examiner alleges that Benkirane remedies this deficiency by teaching that "changing the amino acids within an antigenic peptide from an L-residue to the corresponding D-residue drastically increases the antigeniciity of the peptide and contributes to the generation of high levels of IgG_3 antibodies in immunized animals." (*See* Office Action, page 7). The Examiner concludes that it would have been obvious to a person of ordinary skill in the art to make a vaccine composition using peptides composed of D-amino acids. (*See* Office Action, pages 11-12).

Applicants respectfully traverse the present basis for rejecting Claim 4 under 35 U.S.C. § 103(a). Claim 4 recites "[t]he composition of Claim 3, wherein all amino acid residues are D-amino acids." As noted above, by the present Amendment, Claim 3 is amended to replace the open ended language "comprises" with the closed language "consists of." Accordingly, the isolated prion proteins of Claim 3 do not read on and, therefore, are not anticipated by a full length prion protein. Thus, the present amendments obviate the rejection of instant Claim 3 over Bachmann in view of Gizurarson. Because Benkirane neither teaches nor suggests the isolated prion proteins recited in Claim 3, Benkirane fails to remedy this deficiency in the Bachmann and Gizurarson references. Therefore, Claim 4 must by non-obvious over the combination of Bachmann and Gizurarson in view of Benkirane.

Applicants respectfully request reconsideration and withdrawal of the present basis for rejection of Claim 4 over Bachmann and Gizurarson in view of Benkirane.

Claims 9 and 10 stand rejected as allegedly obvious over Bachmann and Gizurarson as applied to Claim 1 further in view of U.S. Patent Nos. 6,440,423 ["Clements"] and 6,585,975 ["Kleanthous"]. The Examiner cites Clements for allegedly teaching cholera toxin subunit B (CT-B) as an effective adjuvant, and cites Kleanthous for allegedly teaching the covalent attachment of CT-B to antigenic proteins (*see* Office Action, page 8). Clements is also cited for allegedly teaching oral (*i.e.* mucosal) vaccines that simulate IgA and IgM antibody responses. (*See* Clements, col. 1, lines 35-38).

Applicants respectfully traverse the present basis for rejecting Claims 9 and 10 under 35 U.S.C. § 103(a). Claim 9, as presently amended, recites, *inter alia*, "[t]he composition of

Claim 1, wherein the antigen carrier or delivery vehicle is cholera toxin subunit B (CT-B)..." and Claim 10 recites "[t]he composition of Claim 9, wherein the prion protein is covalently attached to the cholera toxin subunit B."

The deficiencies of Bachmann and Gizurarson with respect to instant Claim 1 are discussed above. Namely, Bachmann and Gizurarson fail to teach or suggest compositions comprising an isolated mammalian prion protein, or any other self-antigen, in combination with alum and that such compositions would be effective in eliciting a humoral (*i.e.* IgA) response when administered mucosally.

Clements and Kleanthous fail to remedy any of the deficiencies of Bachmann and Gizurarson. On the contrary, Clements and Kleanthous teach the coupling of a non-self antigen (*i.e.* a foreign antigen) to a host for the purposes of eliciting an immune response against a pathogenic microbe. Neither of these references teach or suggest the coupling of a self-antigen to a host. Moreover, Kleanthous only teaches the eliciting of a Th1 response through parenteral administration. This reference neither teaches nor suggests that a Th2-mediated (*i.e.* humoral) IgA response could be elicited by the mucosal administration of the disclosed complexes. In fact, and as discussed above, at the time of the presently Claimed invention, it was believed in the art that tolerance to a self-antigen could not be overcome through mucosal administration. (See, Czerkinsky).

Applicants respectfully request reconsideration and withdrawal of the present basis for rejection of Claims 9 and 10 over Bachmann and Gizurarson in view of Clements and Kleanthous.

Claims 20, 22, 28, and 45 stand rejected as allegedly obvious over Bachmann, Gizurarson, and U.S. Patent No. 5,733,760 ("Lu") in view of Chabalgoity *et al.*, *Vaccine* 19:460-469 (2000) ("Chabalgoity"). Bachmann and Gizurarson are cited for allegedly teaching "composition[s] comprising a mammalian prion protein formulated for mucosal administration ... wherein the prion protein sequence is identical with the presently claimed SEQ ID NO: 4... ." The Examiner concedes that Bachmann's prion protein "is comprised within the viral like particle and not the attenuated *Salmonella typhi* bacterium transfected spp strain as required by the present claims." The Examiner alleges that Lu remedies this deficiency in Bachmann and

Gizurarson by teaching "vaccine compositions comprising attenuated *Salmonella* vectors expressing heterologous DNA encoding viral antigens from HIV and HCV viruses." The Examiner concedes that Lu "does not teach the specific *Salmonella* strains as recited in the present claim 28" but alleges that Chabalgoity remedies this deficiency by teaching "*Salmonella typhimurium* LVR01 strain expressing heterologous antigens encoding binding fatty acid protein from *Echinococcus granulosus*." (*See* Office Action, page 10).

Applicants respectfully traverse the present basis for rejecting Claims 20, 22, 28, and 45 under 35 U.S.C. § 103(a). Independent Claim 20, as presently amended, is directed to compositions comprising an attenuated *Salmonella typhii* bacterium transfected spp strain transformed with a vector capable of expressing an isolated mammalian prion protein, wherein: the isolated mammalian prion protein is selected from the group consisting of bovine, deer, elk, and sheep prion protein; wherein the composition is suitable for mucosal administration; and the composition elicits a humoral immune response that is predominantly associated with an IgA response and any concomitant immunoglobulin counterpart in other bodily fluids when introduced to a mammalian mucosal immune system. Each of Claims 22, 28, and 45 depend from and contain each of the limitations of independent Claim 20. Thus, the non-obviousness of Claims 22, 28, and 45 necessarily follows from the non-obviousness of independent Claim 20.

Certain deficiencies in Bachmann and Gizurarson, discussed above with respect to independent Claim 1, are also applicable to instant Claim 20. Namely: (1) Bachmann is directed to conjugates that include a prion protein (PrP) and a virus-like particle (VLP), but teaches away from compositions comprising an isolated mammalian prion protein; (2) Bachmann is silent about eliciting an IgA response by the mucosal administration of an isolated mammalian prion protein; (3) Gizurarson teaches the mucosal delivery of compositions comprising a glyceride and a non-self (*i.e.* foreign) antigen, but is silent about compositions comprising a prion protein or any other self antigen; and (4) with respect to Claim 22, neither Bachmann nor Gizurarson teach or suggest the sequences represented by residues 93-156 and 123-225 of the SEQ ID NO: 4. Furthermore, neither Bachmann nor Gizurarson teach or suggest the expression of a prion protein in an attenuated *Salmonella typhii* bacterium transfected spp strain. Thus, instant Claims 20, 22, 28, and 45 cannot be obvious over the combination of Bachmann and Gizurarson.

Lu and Chabalgoity fail to remedy the deficiencies noted in the Bachmann and Gizurarson references. Lu is directed generally to the delivery of a foreign antigen such as from a bacterium, a virus, or a parasite. For example, Lu teaches the use of *Salmonella* to obtain a protective response against a mucosally transmitted infectious agent (*i.e.* a foreign antigen). Lu is silent about the use of a self-antigen such as an isolated mammalian prion protein. Similarly, Chabalgoity teaches the use of *Salmonella* for the delivery of a foreign antigen; Chabalgoity is silent about the delivery of a self-antigen, such as an isolated mammalian prion protein.

As described above, one skilled in the art at the time of the present invention would have believed that the mucosal administration of a self-antigen, such as a prion protein, would have led to immunological tolerance and would not have elicited a Th2-mediated IgA response. There is nothing within the teachings of Lu and/or Chabalgoity that contradicts this dogma. Thus, the combination of Bachmann, Gizurarson, Lu, and Chabalgoity, in view of the state of the art as exemplified by the teachings of Czerkinsky, would have taught one skilled in the art away from the use of any *Salmonella* strain for the expression of an isolated mammalian prion protein to elicit an IgA response through mucosal administration.

Applicants respectfully request reconsideration and withdrawal of the present basis for rejection of Claims 20, 22, 28, and 45 over Bachmann and Gizurarson in view of Lu, and Chabalgoity.

Claims 23 and 46 stand rejected as allegedly obvious over Bachmann and Gizurarson further in view of Lu and Benkirane. The Examiner contends that Bachmann and Lu disclose vaccines that include attenuated *Salmonella typhii* transfected with a vector capable of expressing mammalian prion proteins, and Benkirane discloses the use of D-amino acid peptides to improve antigenicity. The Examiner concludes that it would have been obvious to provide a composition that induces an immune response wherein the antigenic peptides are composed of D-amino acids. (*See* Office Action, page 12).

Claim 23 depends from and further limits dependent Claim 22 and independent Claim 20 and Claim 46 depends from and further limits dependent Claim 45 and independent Claim 20 by reciting that "all amino acid residues are D-amino acids." The non-obviousness of Claims 20, 22, and 45 over Bachmann and Gizurarson is discussed above. Namely: (1) Bachmann is

directed to conjugates that include a prion protein (PrP) and a virus-like particle (VLP), but teaches away from compositions comprising an isolated mammalian prion protein; (2) Bachmann is silent about eliciting an IgA response by the mucosal administration of an isolated mammalian prion protein; (3) Gizurarson teaches the mucosal delivery of compositions comprising a glyceride and a non-self (*i.e.* foreign) antigen, but is silent about compositions comprising a prion protein or any other self antigen; and (4) with respect to Claim 22, neither Bachmann nor Gizurarson teach or suggest the sequences represented by residues 93-156 and 123-225 of the SEQ ID NO: 4.

Neither Lu nor Benkirane remedy these deficiencies in Bachmann and Gizurarson. Furthermore, Lu neither teaches nor suggest compositions comprising an attenuated *Salmonella* strain for the delivery of a self-antigen, such as an isolated mammalian prion protein, to achieve a Th2-mediated humoral IgA immune response. Thus, it is immaterial whether Benkirane discloses the use of D-amino acids peptides to improve antigenicity because such a disclosure fails to overcome the deficiencies noted in the combination of Bachmann and Gizurarson.

Applicants respectfully request reconsideration and withdrawal of the present basis for rejection of Claims 23 and 46 over Bachmann and Gizurarson in view of Lu and Benkirane.

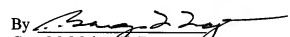
Conclusion

In view of the above remarks, it is respectfully requested that the application be reconsidered and that all pending Claims be allowed and the case passed to issue.

If there are any other issues remaining that the Examiner believes can be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: January 15, 2009

Respectfully submitted,

By 

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